

IN THE CLAIMS

Please amend the claims as follows:

Claim 1 (Withdrawn): A method for evolving an X protein encoded by a *Lactobacillus fermentum* (*L. fermentum*) *ntd* gene to modify its characteristics, comprising the following steps:

- a) obtaining mutants of the *L. fermentum* *ntd* gene by random mutagenesis;
- b) transforming cells comprising a [P-] phenotype with vectors comprising the mutated nucleic acid obtained in step a) coding for the thus modified X* proteins, P-meaning that said cells are auxotrophic for the substance P, P being the product of the action of X on its natural substrate S;
- c) culturing said cells in a medium comprising a substrate S*,
S* being an analogue of the natural substrate S of said X protein; and
- d) selecting the cells [P-:: X*] that have survived step c) in which the X* proteins are capable of carrying out the biosynthesis of the product P from the substrate S*.

Claim 2 (Withdrawn): The method according to claim 1, wherein the mutant X* protein obtained is a protein possessing an activity similar to said protein X, i.e. belonging to the same or adjacent enzyme classes having at least the first three figures 2.4.2 of the EC 4-figure international nomenclature classes.

Claim 3 (Withdrawn): The method according to claim 1, wherein the cells used in step b) are obtained by the inactivation of at least one gene involved in the natural metabolic pathway leading to the product P.

Claim 4 (Withdrawn): The method according to claim 3, wherein the protein X* complements the deficiency of the natural metabolic pathway leading to the product P in a medium provided with the substrate S*.

Claim 5 (Withdrawn): The method according to claim 1, wherein the activity of the protein X on the substrate S is at least two times greater than its activity on the substrate S*.

Claim 6 (Withdrawn): The method according to claim 1, wherein the activity of the protein X* on the substrate S* is at least 10 times greater than its activity on the substrate S.

Claim 7 (Withdrawn): The method according to claim 1, wherein the random mutagenesis of step a) is carried out either by variation of the manganese concentration during the PCR reaction, or by the use of promutagenic nucleotide analogues or also by the utilization of primers comprising a random sequence.

Claim 8 (Withdrawn): The method according to claim 1, wherein said cells are prokaryotic or eukaryotic cells, preferably *E. coli*.

Claim 9 (Withdrawn): The method according to claim 1, wherein an N-deoxyribosyl transferase (DTP) of *L. fermentum* is evolved to obtain a protein is an N-dideoxyribosyl transferase by the following steps:

- a) obtaining DTP* mutants of the sequence coding for an N-deoxyribosyl transferase (DTP) by random mutagenesis;
- b) transforming cells comprising an [N-] phenotype with vectors comprising the mutated nucleic acid obtained in step a) coding for the DTP* proteins, N- meaning that said

cells are auxotrophic for at least one nucleoside, said nucleoside being the product of the action of DTP on its natural substrate dR-N;

c) culturing said cells in a medium comprising a ddR-N substrate; and

d) selecting the [N-:: DTP*] cells that have survived step c) in which the DTP* proteins are capable of carrying out the transfer of the dideoxyribose (ddR) from a dideoxyribonucleoside to another nucleoside leading to the production of the N nucleoside necessary for the survival of the cells.

Claim 10 (Withdrawn): The method according to claim 9 wherein the (ntd) sequence encoding the N-deoxyribosyl transferase (DTP) of *L. fermentum* corresponds to SEQ ID No. 1 which is being evolved.

Claim 11 (Withdrawn): The method according to claim 9, wherein the cells used in step b) are bacteria of genotype $\Delta pyrC$, $\Delta codA$, Δcdd deficient in the metabolic pathway leading to uracil.

Claim 12 (Withdrawn): The method according to claim 11, wherein the bacteria of genotype $\Delta pyrC$, $\Delta codA$, Δcdd deficient in the metabolic pathway leading to uracil used are *E. coli*.

Claim 13 (Currently Amended): A ~~method~~ N-deoxyribosyl transferase protein (DTP) that has at least 90% identity with the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4, but which is not SEQ ID NO: 2;

that retains residues Y13, D77, D97, E103, and M312 that respectively correspond to positions 13, 77, 97, 103, and 132 of SEQ ID NO: 2; and

that has threonine at a position corresponding to position 15 of SEQ ID NO: 2 or SEQ ID NO: 4

~~from the method according to claim 1, wherein the protein has a modified activity.~~

Claim 14 (Currently Amended): The protein according to claim 13, which is at least 95% identical with SEQ ID NO: 2 ~~the protein has an N-dideoxyribosyl transferase activity and/or an activity on deoxy or dideoxyribonucleoside analogues comprising a modified base.~~

Claim 15 (Currently Amended): The protein according to claim 13 ~~wherein the protein has a sequence at least 70%~~ which is at least 95% identical to SEQ ID NO: 4

~~SEQ ID No. 2 and contains the residues Y13, D77, D97, E103, M132.~~

Claim 16 (Currently Amended): The protein according to claim ~~[[15]]~~ 13, which is at least 95% identical to SEQ ID NO: 4

~~wherein the protein has a sequence identity with SEQ ID No. 2 greater than or equal to 80%.~~

Claim 17 (Currently Amended): The protein according to claim 13, which comprises SEQ ID NO: 2, but which does not consist of SEQ ID NO: 2 ~~having an N-dideoxyribosyl transferase activity according to claim 14, wherein the sequence comprises SEQ ID No.4.~~

Claim 18 (Currently Amended): The protein according to claim 13, which comprises SEQ ID NO: 4

~~A protein having an activity on deoxy- or dideoxyribonucleoside analogues, having a percentage identity with SEQ ID No. 4 equal to or greater than 70%, and comprising a threonine residue corresponding to the mutation point A15T of SEQ ID No. 4.~~

Claims 19-20 (Cancelled)

Claim 21 (Currently Amended): The protein according to claim [[18]] 13, wherein said protein which has [[an]] a N-dideoxyribosyl transferase activity.

Claim 22 (Currently Amended): The protein according to claim [[18]] 13, wherein said protein has a deoxyribose and dideoxyribose and/or didehydroribose transfer activity.

Claim 23 (Currently Amended): The protein according to claim [[18]] 13, wherein said protein has a catalytic activity on d4T and ddT greater than that of the native N-deoxyribosyl transferase protein of *L. fermentum* represented by SEQ ID NO: 2 ~~SEQ ID No. 2~~.

Claim 24 (Currently Amended): The protein according to claim 23, wherein said catalytic activity on d4T and ddT is 50% greater than that of the native N-deoxyribosyl transferase protein of *L. fermentum* represented by SEQ ID NO: 2 ~~SEQ ID No. 2~~.

Claim 25 (Currently Amended): The protein according to claim [[18]] 13, wherein said protein has a catalytic effectiveness on d4T and ddT greater than that of the native N-deoxyribosyl transferase protein of *L. fermentum* represented by SEQ ID NO: 2 ~~SEQ ID No. 2~~.

Claim 26 (Currently Amended): The protein according to claim 25, wherein said catalytic effectiveness on d4T and ddT is at least 5 times greater than that of the native N-deoxyribosyl transferase protein of *L. fermentum* represented by SEQ ID NO: 2 ~~SEQ ID No. 2~~.

Claim 27 (Currently Amended): The protein according to claim ~~[[19]]~~ 13, wherein the protein consists of a polypeptide of sequence SEQ ID NO: 4 ~~SEQ ID No. 4~~.

Claim 28 (Currently Amended): An isolated or purified nucleic acid that encodes the protein according to claim 13 ~~comprising a sequence coding for a protein having an N-dideoxyribosyl transferase activity according to claim 13, such as the sequence~~ SEQ ID No. 3.

Claim 29 (Currently Amended): An expression vector comprising ~~[[a]]~~ the nucleic acid according to claim 28.

Claim 30 (Currently Amended): The vector according to claim 29, further comprising a promoter effective in a eukaryotic or prokaryotic cell for expressing said nucleic acid ~~wherein the nucleic acid is fused to an effective promoter for the expression of said coding sequence in the eukaryotic and/or prokaryotic cells.~~

Claim 31 (Currently Amended): The vector according to claim 29, ~~wherein the vector~~ which is a plasmid capable of transforming and being maintained in *E. coli*.

Claim 32 (Previously Presented): A host cell comprising a vector according to claim 29.

Claim 33 (Withdrawn, Currently Amended): A method for transferring a dideoxyribose (ddR) from a dideoxynucleoside to another nucleoside, comprising:
contacting the dideoxynucleoside with a protein having an N-dideoxyribosyl transferase activity according to claim 13.

Claim 34 (Withdrawn, Currently Amended): The method according to claim 33, further comprising synthesizing a used-in-the-synthesis of 2',3'-dideoxynucleoside[[s]].

Claim 35 (Withdrawn, Currently Amended): The method according to claim 33, further comprising synthesizing a used-in-the-synthesis of 2',3'-didehydro-2',3'-dideoxynucleoside[[s]].

Claim 36 (Withdrawn, Currently Amended): A method for preparing a nucleoside[[s]] or a nucleotide analogue[[s]] ~~possessing anti-tumor properties~~, comprising:
expressing the N-deoxyribosyl transferase protein (DTP) encoded by the
using the host cell according to claim 32 for a time and under conditions suitable for
preparing a nucleoside or nucleotide analogue possessing an anti-tumor property.

Claim 37 (Withdrawn, Currently Amended): The method according to claim 36, wherein said nucleoside or nucleotide analogue is for the preparation of ddI ddI or ddC.

Claim 38 (Withdrawn, Currently Amended): A method for preparing a compound comprising contacting a substrate with the protein according to claim 13 ~~the preparation of compounds comprising a step consisting of using a mutated protein according to claim 13.~~

Claim 39 (Withdrawn, Currently Amended): The method according to claim 38, wherein said compound is for the preparation of a nucleoside or a nucleotide analogue[[s]] useful for the treatment of cancer or an infectious disease[[s]], ~~such as a~~ dideoxyribonucleoside[[s]], ~~such as ddC, and ddI~~ ddI or a didehydro-dideoxyribonucleoside[[s]].

Claim 40 (Previously Presented): A strain of *E. coli* deposited at the CNCM on 22nd March 2004 under accession number I-3192.